

TRANSLATION

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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| Applicant's or agent's file reference C1-A0322P | FOR FURTHER ACTION | See Form PCT/IPEA/416 |
| International application No. PCT/JP2004/018499 | International filing date (day/month/year) 10.12.2004 | Priority date (day/month/year) 12.12.2003 |
| International Patent Classification (IPC) or national classification and IPC C07K16/28, A61K39/395, C12N15/13, C12P21/08 | | |
| Applicant CHUGAI SEIYAKU KABUSHIKI KAISHA | | |

| | |
|---|--|
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input type="checkbox"/> (sent to the applicant and to the International Bureau) a total of _____ sheets, as follows:</p> <p><input type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) _____, containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> | |
| <p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the report</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p> | |

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|---|-----------------------------------|
| Date of submission of the demand | Date of completion of this report |
| Name and mailing address of the IPEA/JP | Authorized officer |
| Facsimile No. | Telephone No. |

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/JP2004/018499

Box No. I

Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following _____ which is the language of a translation furnished for the purposes of:
- ☐ international search (Rule 12.3 and 23.1(b))
- ☐ publication of the international application (Rule 12.4)
- ☐ international preliminary examination (Rule 55.2 and/or 55.3)
2. With regard to the elements of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:
- ☒ the international application as originally filed/furnished
- ☐ the description:
- pages _____ as originally filed/furnished
- pages* _____ received by this Authority on _____
- pages* _____ received by this Authority on _____
- ☐ the claims:
- nos. _____ as originally filed/furnished
- nos.* _____ as amended (together with any statement) under Article 19
- nos.* _____ received by this Authority on _____
- nos.* _____ received by this Authority on _____
- ☐ the drawings:
- sheets _____ as originally filed/furnished
- sheets* _____ received by this Authority on _____
- sheets* _____ received by this Authority on _____
- ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (specify): _____
- ☐ any table(s) related to sequence listing (specify): _____
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages _____
- ☐ the claims, nos. _____
- ☐ the drawings, sheets/figs _____
- ☐ the sequence listing (specify): _____
- ☐ any table(s) related to sequence listing (specify): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

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International application No.

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| Box No. V | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement | | |
|-------------------------------|---|------|-----|
| 1. Statement | | | |
| Novelty (N) | Claims | 1-14 | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | | YES |
| | Claims | 1-14 | NO |
| Industrial applicability (IA) | Claims | 1-14 | YES |
| | Claims | | NO |

2. Citations and explanations (Rule 70.7)

Document 1: WO 02/33072 A1 (Chugai Pharmaceutical Co., Ltd.), 25 April 2002

Document 2: WO 02/33073 A1 (Chugai Pharmaceutical Co., Ltd.), 25 April 2002

The invention set forth in claims 1 to 14 does not involve an inventive step in the light of documents 1 and 2 cited in the international search report.

Documents 1 and 2 set forth a modified antibody having an L chain V domain and an H chain V domain which forms the same antigen bonding domain as a new antibody which effectively does not have a TPO agonist activity and which bonds to a TPO receptor, as a modified antibody having TPO agonist activity, and suggest that said modified antibody includes antibodies having an agonist effect (see document 1, page 5, lines 17 to 25; document 2, page 5, lines 6 to 15).

Moreover, a modified antibody containing two or more L chain V domains and two or more H chain V domains of a new antibody such as sc(Fv)₂ was a known feature at the priority date of this application (see, for example, J. Immunol. Methods, 1999, Vol. 231 (No. 1-2), pages 177 to 189, WO 01/79494 A1, WO 01/66737 A1).

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Box No. V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability;
citations and explanations supporting such statement

In the light of said suggestion of documents 1 and 2, it would be easy for a person skilled in the art to conceive of measuring the bonding activity of sample antibodies, selecting a new antibody having bonding activity, using known genetic engineering techniques to prepare modified antibodies having the pair of H chain V domain and L chain V domain of said new antibodies, measuring the agonist activity of said modified antibodies, and selecting a modified antibody having agonist activity.

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Supplemental Box Relating to Sequence Listing

Continuation of Box No. I, item 2:

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this report was established on the basis of:
 - a. type of material
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material
 - ☐ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing
 - ☒ contained in the international application as filed
 - ☐ filed together with the international application in computer readable form
 - ☐ furnished subsequently to this Authority for the purposes of search and/or examination
 - ☐ received by this Authority as an amendment* on _____
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

* If item 4 in Box No. I applies, the listing and/or table(s) related thereto, which form part of the basis of the report, may be marked "superseded."